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material to cells *in vitro*, for example, for gene therapy and for delivery of drugs to cells *in vivo*. Delivery of the agents, or disruption of the membrane to release cell or organelle contents can also be achieved by adjusting the pH, for example, by adding acid to the environment of the cells or organelles, to trigger

5   membrane disruption.

Brief Description of the Drawings

Figure 1 is a schematic of the synthesis of a conjugate of a hydrophobic polymeric backbone having PEG (MW 5000) coupled thereto. As depicted, the hydrophobic polymer includes a hydrophobic backbone and at least one side

10   chain which increases water solubility, and a pH unstable linker. The PEG is coupled via a acetyl bond on the pH unstable linker to the hydrophobic polymer.

Figure 2 is a graph of the percent hemolysis by the conjugate of Figure 1 at pH 5.0 (squares) compared to lysis at pH 7.4 (diamonds) as a function of the amount of polymer (micrograms).

15   Figure 3 is a schematic of three polymer conjugates. The drug is connected to the membrane disruptive polymer backbone in a number of different manners, including directly, via PEG groups, via disulfide linkages, or via PEG-disulfide groups through the use of acid degradable linkages. This figure also depicts how the drug is delivered to the cytoplasm.

20   Figure 4 shows the chemical structure of three embodiments of the described compositions, Polymer E1, Polymer E2 and Polymer E3. In each of these compositions, the membrane-disruptive backbone is a terpolymer of butyl methacrylate (BMA), dimethylaminoethyl methacrylate (DMAEMA) and styrene benzaldehyde.

25   Figures 5A and 5B are a schematic of the synthesis of the composition depicted in Figure 4.

Figure 6A is a graph of the pH-dependent hydrolysis of Polymer E1. Percent hydrolysis versus time (minutes) is plotted for pH 5.4 (squares) and pH 7.4 (stars).

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degree of hemolysis was determined by measuring absorbance of the supernatant at 541 nM. A 100% lysis was determined by lysing the red blood cells in deionized water. The controls were RBCs suspended in buffer without polymer. Experiments were done in triplicate with a standard deviation of less

5   than 2%.

The results of the hemolysis assay are shown in Figure 2. The polymer caused 100% lysis at the lowest concentration tested, five micrograms of polymer at pH 5.0 and unmeasurable lysis at pH 7.4.

Example 2:   Synthesis of Compositions containing a terpolymer of
10   **dimethylaminoethyl methacrylate, butyl methacrylate and**
                styrene benzaldehyde for pH mediated disruption of
                membranes.

A terpolymer of dimethylaminoethyl methacrylate (DMAEMA), butyl methacrylate (BMA) and styrene benzaldehyde was chosen for the membrane-
15   disruptive backbone (see Figure 4). Copolymers of BMA and DMAEMA are extremely effective membrane disruptive agents, a property that can be attributed to their cationic and hydrophobic components, leading to a surfactant-like character. C. Hansch, W. R. Glave, Mol. Pharmacol, 7:337 (1972).

The strategy used to synthesize the compositions is depicted in Figures 5A
20   and 5B. The first step was the synthesis of a functionalized acetal monomer. This monomer was then copolymerized with DMAEMA and BMA using a free radical polymerization process. The resulting terpolymer was purified by precipitation in hexane and then PEGylated with thiol-terminated monofunctional or heterobifunctional PEGs. The PEGylated polymers were purified by ether precipitation. The acid-
25   degradable linkage is a para-amino benzaldehyde acetal. The PEG grafts have a molecular weight of 5kD. Three different compositions were formed from the PEGylated terpolymer; Polymer E1, in which the PEG grafts are terminated with a methoxy group, Polymer E2, in which the PEG grafts are terminated with lactose or, fluorescein-isothiocynate (FITC), and Polymer E3, in which the PEG grafts are
30   terminated with lactose or hexalysine. The chemistry described herein to conjugate drug molecules can be easily modified to incorporate a variety of other conjugation strategies (see Figure 3 for examples).